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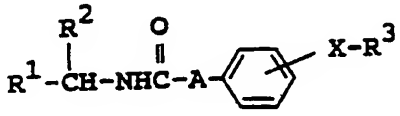
(54) Title: NEW AMIDE DERIVATIVES



(I)

(57) Abstract

This invention relates to new amide derivatives having an inhibitory activity against acyl-CoA: cholesterol acyltransferase enzyme and represented by general formula (I), wherein $R^1$ is ar(lower)alkyl, $R^2$ is aryl, $R^3$ is alkyl or alkenyl, A is a single bond, lower alkylene or lower alkenylene, and X is O, S or a single bond, to processes for the preparation thereof and to a pharmaceutical composition comprising the same.

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# DESCRIPTION

## NEW AMIDE DERIVATIVES

### TECHNICAL FIELD

This invention relates to new amide derivatives which are useful as a medicament.

### BACKGROUND ART

Some amide derivatives have been known as useful cholesterol-lowering agents, for example, in U.S. Patent Nos. 3,784,577 and 3,995,059, and EP Patent Application Publication No. 0025569.

### DISCLOSURE OF INVENTION

This invention relates to new amide derivatives.

More particularly, it relates to new amide derivatives which have an inhibitory activity against acyl-CoA : cholesterol acyltransferase enzyme (hereinafter, ACAT), to processes for the preparation thereof, to a pharmaceutical composition comprising the same and to a method for the prevention and/or treatment of hypercholesterolemia, hyperlipidemia, atherosclerosis or diseases caused thereby.

One object of this invention is to provide new and useful amide derivatives which possess an inhibitory activity against ACAT.

Another object of this invention is to provide processes for preparation of said amide derivatives.

A further object of this invention is to provide a pharmaceutical composition comprising, as an active ingredient, said amide derivatives.

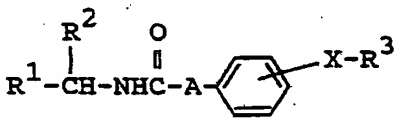
Still further object of this invention is to provide a therapeutical method for the prevention and/or treatment of hypercholesterolemia, hyperlipidemia, atherosclerosis

or diseases caused thereby in human beings or animals, using said amide derivatives.

High levels of blood cholesterol and blood lipids are conditions which are involved in the onset of atherosclerosis.

It is well known that inhibition of ACAT-catalyzed cholesterol esterification could lead to diminish intestinal absorption of cholesterol as well as a decrease in the intracellular accumulation of cholesterol esters in the intima of the arterial wall. Therefore, ACAT inhibitors are useful for the prevention and/or treatment of hypercholesterolemia, hyperlipidemia, atherosclerosis or diseases caused thereby such as cardiac insufficiency (e.g. angina pectoris, myocardial infarction, etc.), cerebrovascular disturbance (e.g. cerebral infarction, cerebral apoplexy, etc.), arterial aneurism, peripheral vascular disease, xanthomas, restenosis after percutaneous transluminal coronary angioplasty, or the like.

The object amide derivatives of this invention are new and can be represented by the following general formula (I) :

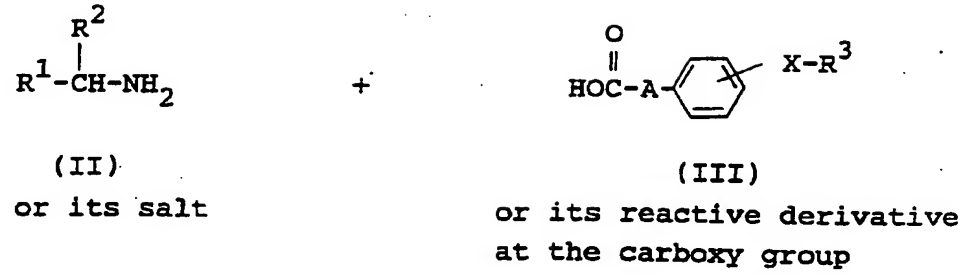


(I)

wherein $R^1$ is ar(lower)alkyl,
$R^2$ is aryl,
$R^3$ is alkyl or alkenyl,
A is a single bond, lower alkylene or lower alkenylene, and
X is O, S or a single bond.

The object compound (I) can be prepared by processes as illustrated in the following reaction schemes.

Process 1



(II)
or its salt

(III)
or its reactive derivative at the carboxy group

Process 2

(Ia) (Ib)

wherein $R^1$, $R^2$, $R^3$, A and X are each as defined above,
$A^1$ is lower alkenylene, and
$A^2$ is lower alkylene.

In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

The lower moiety in the terms "lower alkenylene" and "lower alkenyl" is intended to mean a group having 2 to 6

carbon atoms.

The term "alkyl" may include lower alkyl, higher alkyl and the like.

The term "alkenyl" may include lower alkenyl, higher alkenyl and the like.

Suitable "lower alkyl" may be a straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, or the like, in which preferable one is one having 2 to 6 carbon atoms and the most preferable one is butyl or hexyl.

Suitable "lower alkenyl" may be a straight or branched one such as vinyl, propenyl, butenyl, pentenyl, hexenyl, isopropenyl, or the like.

The term "higher" is intended to mean 7 to 20 carbon atoms, unless otherwise provided.

Suitable "higher alkyl" may be a straight or branched one such as heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, eicosyl, methylheptyl, methyloctyl, methylnonyl, methyldecyl, ethylheptyl, ethyloctyl, ethylnonyl, ethyldecyl or the like, in which preferable one is one having 7 to 12 carbon atoms and the most preferable one is heptyl, octyl, nonyl, decyl, undecyl or dodecyl.

Suitable "higher alkenyl" may be a straight or branched one such as heptenyl, octenyl, nonenyl, decenyl, undecenyl, dodecenyl, tridecenyl, tetradecenyl, pentadecenyl, hexadecenyl, heptadecenyl, octadecenyl, nonadecenyl, eicosenyl, methylheptenyl, methyloctenyl, methylnonenyl, methyldecenyl, ethylheptenyl, ethyloctenyl, ethylnonenyl, ethyldecenyl, or the like, in which preferable one is octenyl, nonenyl or undecenyl.

Suitable "aryl" may be phenyl, naphthyl, phenyl substituted with lower alkyl [e.g. tolyl, xylyl, mesityl, cumenyl, etc.], and the like, in which preferable one is phenyl.

Suitable "ar(lower)alkyl" may be phenyl(lower)alkyl [e.g. benzyl, phenethyl, phenylpropyl, benzhydryl, trityl, etc.], tolyl(lower)alkyl [e.g. tolylmethyl, tolylethyl, etc.], xylylmethyl, mesitylmethyl, cumenylmethyl, and the like, in which preferable one is phenyl(lower)alkyl or tolyl(lower)alkyl and the most preferable one is benzyl or tolylmethyl.

Suitable "lower alkylene" may be a straight or branched one such as methylene, ethylene, trimethylene, propylene, tetramethylene, pentamethylene, hexamethylene, ethylethylene, or the like, in which preferable one is methylene, ethylene or trimethylene.

Suitable "lower alkenylene" may be a straight or branched one such as vinylene, propenylene, butenylene, pentenylene, hexenylene, isopropenylene, or the like, in which preferable one is vinylene.

Preferable compound (I) is one which has ar(lower)alkyl (more preferably phenyl(lower)alkyl) for $R^1$, aryl (more preferably phenyl) for $R^2$, higher alkyl (more preferably one having 7 to 12 carbon atoms) for $R^3$, lower alkylene for A, and O for X.

More preferable compound (I) is one which has benzyl or tolylmethyl for $R^1$, phenyl for $R^2$, heptyl, octyl, nonyl, decyl, undecyl or dodecyl for $R^3$, methylene, ethylene or trimethylene for A, and O for X.

The processes for preparing the object compound (I) are explained in detail in the following.

Process 1

The object compound (I) can be prepared by reacting a compound (II) or its salt with compound (III) or its reactive derivative at the carboxy group.

Suitable salt of the compound (II) may be an acid addition salt such as an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate,

etc.], an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.], or the like.

Suitable reactive derivative of the compound (III) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. The suitable example may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid etc.), dialkylphosphorus acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid (e.g. methanesulfonic acid, etc.), alkylcarbonic acid, aliphatic carboxylic acid (e.g. pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid or trichloroacetic acid, etc.) or aromatic carboxylic acid (e.g. benzoic acid, etc.); a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester (e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2\overset{+}{N}=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.), or an ester with a N-hydroxy compound (e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, 1-hydroxy-6-chloro-1H-benzotriazole, etc.) and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (III) to be used.

The reaction is usually carried out in a conventional solvent such as water, alcohol (e.g. methanol, ethanol, etc.), acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

When the compound (III) is used in free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phohsphorus trichloride; thionyl chloride; oxalyl chloride; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intra-molecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorphorine, N,N-di(lower)alkylbenzylamine, or the like. The reaction temperature is not critical, and the reaction is preferably carried out under cooling

or at ambient temperature.

Process 2

The object compound (Ib) can be prepared by subjecting a compound (Ia) to reduction.

The present reduction is carried out by chemical reduction, catalytic reduction, or the like.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalyst [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalyst [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel catalyst [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalyst [e.g. reduced cobalt, Raney cobalt, etc.], iron catalyst [e.g. reduced iron, Raney iron, etc.], copper catalyst [e.g. reduced copper, Raney copper, Ullman copper, etc.] or the like.

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, an alcohol [e.g. methanol, ethanol, propanol, etc.], N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be

the above-mentioned solvent and other conventional solvent such as diethyl ether, methylene chloride, dioxane, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to heating.

In this reaction, in case that the compound (Ia) having alkenyl for $R^3$ is used as a starting compound, the compound (Ib) having alkyl for $R^3$ may be obtained according to reaction conditions. This case is included within the scope of the present reaction.

The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, or the like.

It is to be noted that the compound (I) and the other compounds may include one or more stereoisomers due to asymmetric carbon atom(s), and all of such isomers and mixture thereof are included within the scope of this invention.

The object compounds (I) possess an strong inhibitory activity against ACAT, and are useful for the prevention and/or treatment of hypercholesterolemia, hyperlipidemia, atherosclerosis or diseases caused thereby.

In order to illustrate the usefulness of the object compound (I), the pharmacological test data of some representative compounds of the compound (I) are shown in the following.

Test compounds :

(a) rac-N-(1,2-Diphenylethyl)-3-(2-heptyloxyphenyl)-propionamide

(b) rac-N-(1,2-Diphenylethyl)-3-(4-heptyloxyphenyl)-propionamide

(c) rac-N-(1,2-Diphenylethyl)-2-octyloxyphenylacetamide

(d) rac-N-[2-(4-Methylphenyl)-1-phenylethyl]-2-octyloxyphenylacetamide

(e) rac-N-[2-(4-Methylphenyl)-1-phenylethyl]-2-nonyloxyphenylacetamide

(f) rac-N-(1,2-Diphenylethyl)-2-decyloxyphenylacetamide

(g) rac-(E)-N-[2-(4-Methylphenyl)-1-phenylethyl]-2-(2-octenyloxy)phenylacetamide

Test :

Acyl-CoA : cholesterol acyltransferase (ACAT) inhibitory activity

Method :

ACAT activity was measured by the method of Heider et al. described in Journal of Lipid Research, Vol. 24, page 1127 (1983). The enzyme ACAT was prepared from the mucosal microsome fraction of the small intestine of male, 18-week old Japanese white rabbits which had been feeded diet containing 2% cholesterol for 8 weeks. The inhibitory activity of compounds were calculated by measuring the amount of the labeled cholesterol ester produced from [$^{14}$C]oleoyl-CoA and endogenous cholesterol as follows. [$^{14}$C]oleoyl-CoA and microsome were incubated with test compounds at 37°C for 5 minutes. The reaction was stopped by the addition of chloroform-methanol (2:1, V/V). Cholesterol ester fraction in the chloroform-methanol extracts was isolated by thin-layer chromatography and was counted their label.

Results

| Test Compound | $IC_{50}$(M) |
|---|---|
| (a) | $2.6 \times 10^{-8}$ |
| (b) | $6.4 \times 10^{-8}$ |
| (c) | $9.4 \times 10^{-8}$ |
| (d) | $2.9 \times 10^{-8}$ |
| (e) | $3.0 \times 10^{-8}$ |
| (f) | $3.2 \times 10^{-8}$ |
| (g) | $9.1 \times 10^{-8}$ |

For therapeutic purpose, the compound (I) of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external (topical) administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, suppositories, solution, lotion, suspension, emulsion, ointment, gel, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of the compound (I) will vary depending upon the age and condition of the patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg,

100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating the above-mentioned diseases. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

The following Preparations and Examples are given for the purpose of illustrating this invention.

Preparation 1

To a stirred mixture of 3-hydroxyphenylacetic acid (1.52 g) and aqueous 10% sodium hydroxide solution (8 ml) in dimethyl sulfoxide (30 ml) was added a solution of 1-iodooctane (2.40 g) in dimethyl sulfoxide (10 ml) dropwise at 80°C and the mixture was stirred at 80°C for 2 hours. After cooling the reaction mixture was poured into 3% hydrochloric acid and extracted with diethyl ether. The ethereal extract was washed with brine, dried and evaporated. Recrystallization from n-hexane gave 3-octyloxyphenylacetic acid (1.93 g).

mp : 76-77°C

IR (Nujol) : 3100, 1680, 1590, 1490, 1400, 1260, 870, 770, 700 $cm^{-1}$

NMR ($CDCl_3$, $\delta$) : 0.88 (3H, t, J=7Hz), 1.22-1.50 (10H, m), 1.70-1.83 (2H, m), 3.58 (2H, s), 3.93 (2H, t, J=7Hz), 6.75-6.85 (3H, m), 7.18-7.28 (1H, m)

The following compounds (Preparations 2-1) to 2-25)) were obtained according to a similar manner to that of Preparation 1.

Preparation 2

1) 3-Heptyloxycinnamic acid

mp : 84-86°C

IR (Nujol) : 3400, 1680, 1620, 1570, 1370, 1300,

1260, 1040 $cm^{-1}$

NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.20-1.48 (8H, m), 1.72-1.88 (2H, m), 3.95 (2H, t, J=7Hz), 6.43 (1H, d, J=15Hz), 6.93 (1H, d, J=7Hz), 7.07-7.19 (2H, m), 7.32 (1H, t, J=8Hz), 7.75 (1H, d, J=15Hz)

2) 4-Octyloxyphenylacetic acid

mp : 76-78°C

IR (Nujol) : 3100, 1680, 1600, 1400, 1300, 1240, 1040, 620 $cm^{-1}$

NMR ($CDCl_3$, δ) : 0.85 (3H, t, J=7Hz), 1.23-1.47 (10H, m), 1.70-1.85 (2H, m), 3.55 (2H, s), 3.92 (2H, t, J=7Hz), 6.85 (2H, d, J=10Hz), 7.18 (2H, d, J=10Hz)

3) 2-Octyloxyphenylacetic acid

IR (Neat) : 3030, 2930, 1700, 1600, 1500, 1455, 1240, 745 $cm^{-1}$

NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=7Hz), 1.20-1.48 (10H, m), 1.78 (2H, t, J=7Hz), 3.63 (2H, s), 3.98 (2H, t, J=7Hz), 6.81-6.95 (2H, m), 7.17-7.30 (2H, m)

4) 4-Nonyloxybenzoic acid

mp : 90-92°C

IR (Nujol) : 1670, 1600, 1300, 1250, 840, 760 $cm^{-1}$

NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.20-1.52 (12H, m), 1.81 (2H, t, J=7Hz), 4.03 (2H, t, J=7Hz), 6.93 (2H, d, J=8Hz), 8.05 (2H, d, J=8Hz)

5) 4-Decyloxyphenylacetic acid

mp : 75-76°C

IR (Nujol) : 3050, 1680, 1520, 1400, 1300, 1250,

1180, 1030, 900, 830, 790, 720 $cm^{-1}$
NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=7Hz), 1.22-1.48 (14H, m), 1.70-1.82 (2H, m), 3.59 (2H, s), 3.95 (2H, t, J=7Hz), 6.85 (2H, d, J=8Hz), 7.18 (2H, d, J=8Hz)

6) 2-Heptyloxycinnamic acid
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.33 (8H, m), 1.88 (2H, q, J=7Hz), 4.05 (2H, t, J=7Hz), 6.57 (1H, d, J=15Hz), 6.89-7.00 (2H, m), 7.36 (1H, ddd, J=9, 9, 2Hz), 7.53 (1H, dd, J=9, 2Hz), 8.10 (1H, d, J=15Hz)

7) 4-Heptyloxycinnamic acid
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.30 (8H, m), 1.80 (2H, q, J=7Hz), 4.00 (2H, t, J=7Hz), 6.35 (1H, d, J=15Hz), 6.90 (2H, d, J=9Hz), 7.50 (2H, d, J=9Hz), 7.75 (1H, d, J=15Hz)

8) 2-Decyloxycinnamic acid
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.33 (14H, m), 1.90 (2H, q, J=7Hz), 4.04 (2H, t, J=7Hz), 6.59 (1H, d, J=15Hz), 6.90-7.00 (2H, m), 7.36 (1H, ddd, J=9, 9, 2Hz), 7.55 (1H, dd, J=9, 2Hz), 8.10 (1H, d, J=15Hz)

9) 4-Decyloxycinnamic acid
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.30 (14H, m), 1.80 (2H, q, J=7Hz), 4.00 (2H, t, J=7Hz), 6.30 (1H, d, J=15Hz), 6.90 (2H, d, J=9Hz), 7.50 (2H, d, J=9Hz), 7.70 (1H, d, J=15Hz)

10) 2-Butoxycinnamic acid
NMR ($CDCl_3$, δ) : 1.00 (3H, t, J=7Hz), 1.55 (2H, m), 1.87 (2H, q, J=7Hz), 4.05 (2H, t, J=7Hz),

6.60 (1H, d, J=15Hz), 6.90-7.00 (2H, m), 7.46 (1H, ddd, J=9, 9, 2Hz), 7.55 (1H, dd, J=9, 2Hz), 8.10 (1H, d, J=15Hz)

11) 2-Butoxyphenylacetic acid
NMR ($CDCl_3$, δ) : 0.96 (3H, t, J=7Hz), 1.39-1.56 (2H, m), 1.78 (2H, q, J=7Hz), 3.67 (2H, s), 4.00 (2H, t, J=7Hz), 6.83-6.94 (2H, m), 7.15-7.30 (2H, m)

12) 2-Hexyloxyphenylacetic acid
NMR ($CDCl_3$, δ) : 0.94 (3H, t, J=7Hz), 1.35 (6H, br s), 1.80 (2H, q, J=7Hz), 3.69 (2H, s), 4.00 (2H, t, J=7Hz), 6.83-6.94 (2H, m), 7.16-7.30 (2H, m)

13) 2-Heptyloxyphenylacetic acid
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.30 (8H, br s), 1.79 (2H, q, J=7Hz), 3.65 (2H, s), 3.99 (2H, t, J=7Hz), 6.82-6.94 (2H, m), 7.17-7.40 (2H, m)

14) 4-(4-Heptyloxyphenyl)butyric acid
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.31 (10H, br s), 1.90-1.99 (2H, m), 2.36 (2H, t, J=7Hz), 2.62 (2H, t, J=7Hz), 3.92 (2H, t, J=7Hz), 6.92 (2H, d, J=9Hz), 7.08 (2H, d, J=9Hz)

15) 2-Octyloxyphenylacetic acid
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.30 (10H, br s), 1.78 (2H, q, J=7Hz), 3.68 (2H, s), 3.98 (2H, t, J=7Hz), 6.84-6.94 (2H, m), 7.18-7.30 (2H, m)

16) 4-Octyloxycinnamic acid
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.30 (10H, br s), 1.78 (2H, qui, J=7Hz), 4.00 (2H, t, J=7Hz), 6.32 (1H, d, J=15Hz), 6.91 (2H, d, J=9Hz), 7.51 (2H, d, J=9Hz), 7.75 (1H, d, J=15Hz)

17) 2-Octyloxycinnamic acid
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.35 (10H, br s), 1.87 (2H, q, J=7Hz), 4.05 (2H, t, J=7Hz), 6.57 (1H, d, J=15Hz), 6.89-7.00 (2H, m), 7.30-7.40 (1H, m), 7.53 (1H, dd, J=9, 2Hz), 8.11 (1H, d, J=15Hz)

18) 2-Dodecyloxyphenylacetic acid
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.30 (18H, br s), 1.80 (2H, q, J=7Hz), 3.68 (2H, s), 4.00 (2H, t, J=7Hz), 6.84-6.96 (2H, m), 7.15-7.30 (2H, m)

19) (E)-2-(2-Octenyloxy)phenylacetic acid
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.32 (6H, br s), 2.02-2.12 (2H, m), 3.70 (2H, s), 4.52 (2H, dd, J=7, 2Hz), 5.59-5.90 (2H, m), 6.88-6.98 (2H, m), 7.18-7.29 (2H, m)

20) 2-Nonyloxyphenylacetic acid
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.29 (12H, br s), 1.79 (2H, q, J=7Hz), 3.65 (2H, s), 4.00 (2H, t, J=7Hz), 6.85-6.96 (2H, m), 7.17-7.30 (2H, m)

21) 2-Decyloxyphenylacetic acid
NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=7Hz), 1.27-1.47 (14H, m), 1.76 (2H, q, J=7Hz), 3.66 (2H, s), 3.96 (2H, t, J=7Hz), 6.84-6.93 (2H, m), 7.15-7.29 (2H, m)

22) 2-Heptyloxycinnamic acid
NMR ($CDCl_3$, δ) : 0.91 (3H, t, J=7Hz), 1.30-1.56 (8H, m), 1.85 (2H, q, J=7Hz), 4.03 (2H, t, J=7Hz), 6.58 (1H, d, J=16Hz), 6.90-7.00 (2H, m), 7.35 (1H, ddd, J=8, 8, 2Hz), 7.53 (1H, dd, J=8, 2Hz), 8.12 (1H, d, J=16Hz)

23) 2-Hexyloxyphenylacetic acid

NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.27-1.48 (6H, m), 1.77 (2H, q, J=7Hz), 3.66 (2H, s), 3.97 (2H, t, J=7Hz), 6.83-6.95 (2H, m), 7.17-7.30 (2H, m)

24) 2-Hexyloxycinnamic acid

NMR ($CDCl_3$, δ) : 0.92 (3H, t, J=7Hz), 1.32-1.53 (6H, m), 1.86 (2H, q, J=7Hz), 4.03 (2H, t, J=7Hz), 6.58 (1H, d, J=16Hz), 6.89-6.99 (2H, m), 7.33 (1H, ddd, J=1.5, 8, 8Hz), 7.52 (1H, dd, J=1.5, 8Hz), 8.12 (1H, d, J=16Hz)

25) 4-Hexyloxycinnamic acid

NMR ($CDCl_3$, δ) : 0.91 (3H, t, J=7Hz), 1.30-1.49 (6H, m), 1.78 (2H, q, J=7Hz), 3.99 (2H, t, J=7Hz), 6.32 (1H, d, J=16Hz), 6.91 (2H, d, J=8Hz), 7.49 (2H, d, J=8Hz), 7.75 (1H, d, J=16Hz)

Preparation 3

A solution of 2-hexyloxycinnamic acid (3.74 g) in tetrahydrofuran (50 ml) was hydrogenated over 10% palladium on carbon (0.5 g) at ambient temperature at 1 atm for 4 hours. The catalyst was filtered off and washed with tetrahydrofuran. The filtrate and washings were concentrated under the reduced pressure to leave 3-(2-hexyloxyphenyl)propionic acid (3.4 g).

NMR ($CDCl_3$, δ) : 0.91 (3H, t, J=7Hz), 1.30-1.54 (6H, m), 1.81 (2H, q, J=7Hz), 2.66 (2H, t, J=7Hz), 2.95 (2H, t, J=7Hz), 3.95 (2H, t, J=7Hz), 6.80-6.90 (2H, m), 7.12-7.22 (2H, m)

The following compound (Preparation 4) was obtained according to a similar manner to that of Preparation 3.

Preparation 4

3-(4-Hexyloxyphenyl)propionic acid

NMR ($CDCl_3$, δ) : 0.91 (3H, t, J=7Hz), 1.29-1.47 (6H, m), 1.77 (2H, q, J=7Hz), 2.62 (2H, t, J=7Hz), 2.97 (2H, t, J=7Hz), 3.91 (2H, t, J=7Hz), 6.82 (2H, d, J=8Hz), 7.10 (2H, d, J=8Hz)

Preparation 5

To a stirred solution of decyltriphenylphosphonium bromide (12.9 g) in tetrahydrofuran (25 ml) was added potassium tert-butoxide (2.7 g) at 0°C and the mixture was stirred at 0°C for 30 minutes. To this mixture was added a solution of methyl 3-(4-formylphenyl)propionate (2.6 g) in tetrahydrofuran (20 ml) at 0°C and the mixture was refluxed for 3 hours. After cooling the reaction mixture was poured into aqueous saturated ammonium chloride and extracted with diethyl ether. The extract was washed with water and dried. Evaporation of solvent gave an oily residue which was chromatographed on silica gel. Elution with ethyl acetate-n-hexane (1:10) afforded methyl (Z)-3-[4-(1-undecenyl)phenyl]propionate (741 mg).

NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=7Hz), 1.24 (14H, br s), 2.30 (2H, m), 2.63 (2H, t, J=7Hz), 2.95 (2H, t, J=7Hz), 3.69 (3H, s), 5.58-5.7 (1H, m), 6.37 (1H, d, J=11Hz), 7.10-7.25 (4H, m)

The following compounds (Preparations 6-1) and 6-2)) were obtained according to a similar manner to that of Preparation 5.

Preparation 6

1) Methyl (Z)-3-[4-(1-octenyl)phenyl]propionate

NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=7Hz), 1.28 (8H, br s), 2.18-2.38 (2H, m), 2.63 (2H, t, J=7Hz), 2.96 (2H, t, J=7Hz), 3.69 (3H, s), 5.63 (1H, dt,

J=11, 7Hz), 6.37 (1H, d, J=11Hz), 7.09-7.24 (4H, m)

2) Methyl (Z)-3-[4-(1-nonenyl)phenyl]propionate

NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.29 (10H, br s), 2.27-2.38 (2H, m), 2.63 (2H, t, J=7Hz), 2.95 (2H, t, J=7Hz), 3.70 (3H, s), 5.63 (1H, dt, J=11, 7Hz), 6.36 (1H, d, J=11Hz), 7.09-7.29 (4H, m)

Preparation 7

A mixture of methyl (Z)-3-[4-(1-octenyl)phenyl]-propionate (2.385 g) and 1N sodium hydroxide (17.4 ml) in methanol (30 ml) was stirred at ambient temperature for 4 hours. Methanol was evaporated to leave a residue which was acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with water, dried and evaporated to give (Z)-3-[4-(1-octenyl)phenyl]-propionic acid (2.025 g).

NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=7Hz), 1.28 (8H, br s), 2.15-2.48 (2H, m), 2.71 (2H, t, J=7Hz), 2.98 (2H, t, J=7Hz), 5.64 (1H, dt, J=11, 7Hz), 6.87 (1H, d, J=11Hz), 7.10-7.30 (4H, m)

The following compounds (Preparation 8-1) and 8-2)) were obtained according to a similar manner to that of Preparation 7.

Preparation 8

1) (Z)-3-[4-(1-Undecenyl)phenyl]propionic acid

2) (Z)-3-[4-(1-Nonenyl)phenyl]propionic acid

Example 1

A mixture of 4-butoxyphenylacetic acid (470 mg) and

thionyl chloride (2 ml) was stirred at 100°C for 30 minutes. After cooling excess thionyl chloride was evaporated and removed azeotropically with benzene under reduced pressure to give 4-butoxyphenylacetyl chloride (490 mg). To a stirred solution of rac-1,2-diphenylethylamine (460 mg) and triethylamine (0.4 ml) in chloroform (15 ml) was added a solution of 4-butoxyphenylacetyl chloride (490 mg) in chloroform (5 ml) dropwise at 0°C and the mixture was stirred at 0°C for 30 minutes. The reaction mixture was washed with dilute hydrochloric acid, dilute sodium bicarbonate solution and water, and dried. Evaporation of solvent gave an oily residue which was chromatographed on silica gel. Elution with chloroform gave rac-N-(1,2-diphenylethyl)-4-butoxyphenylacetamide as a crystal (700 mg).

mp : 148°C

NMR ($CDCl_3$, δ) : 1.00 (3H, t, J=7Hz), 1.52 (2H, tq, J=7, 7Hz), 1.80 (2H, tt, J=7, 7Hz), 2.85 (1H, dd, J=7, 14Hz), 3.03 (1H, dd, J=7, 14Hz), 3.44 (2H, s), 3.99 (2H, t, J=7Hz), 5.25 (1H, dt, J=7, 7Hz), 5.68 (1H, d, J=7Hz), 6.83-7.24 (14H, m)

The following compounds (Examples 2-1) to 2-37)) were obtained according to a similar manner to that of Example 1.

Example 2

1) rac-N-(1,2-Diphenylethyl)-2-heptyloxycinnamamide

mp : 105-107°C

NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.30 (8H, m), 1.84 (2H, q, J=7Hz), 3.20 (2H, d, J=7Hz), 4.00 (2H, t, J=7Hz), 5.41 (1H, dt, J=7, 9Hz), 5.83 (1H, d, J=9Hz), 6.48 (1H, d, J=15Hz), 6.90 (2H, ddd, J=9, 9, 2Hz), 7.05-7.30 (11H, m), 7.45 (1H, d, J=9Hz), 7.89 (1H, d, J=15Hz)

2) rac-N-(1,2-Diphenylethyl)-4-heptyloxycinnamamide
mp : 142-144°C
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.30 (8H, m),
1.80 (2H, q, J=7Hz), 3.20 (2H, d, J=7Hz),
3.98 (2H, t, J=7Hz), 5.41 (1H, dt, J=9, 7Hz),
5.82 (1H, d, J=9Hz), 6.20 (1H, d, J=15Hz),
6.85 (2H, d, J=9Hz), 7.07-7.10 (2H, m),
7.20-7.30 (8H, m), 7.40 (2H, d, J=9Hz),
7.52 (1H, d, J=15Hz)

3) rac-N-(1,2-Diphenylethyl)-4-decyloxycinnamamide
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.35 (14H, m),
1.80 (2H, q, J=7Hz), 3.20 (2H, d, J=7Hz),
4.00 (2H, t, J=7Hz), 5.45 (1H, dt, J=9, 7Hz),
5.95 (1H, d, J=9Hz), 6.00 (1H, d, J=15Hz),
6.90 (2H, d, J=9Hz), 7.10-7.35 (10H, m),
7.40 (2H, d, J=9Hz), 7.55 (1H, d, J=15Hz)

4) rac-N-(1,2-Diphenylethyl)-2-decyloxycinnamamide
mp : 85-87.5°C
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.30 (14H, m),
1.85 (2H, q, J=7Hz), 3.20 (2H, d, J=7Hz),
4.00 (2H, t, J=7Hz), 5.40 (1H, dt, J=9, 7Hz),
5.85 (1H, d, J=9Hz), 6.50 (1H, d, J=15Hz),
6.90 (2H, t, J=9Hz), 7.10-7.33 (11H, m),
7.45 (1H, dd, J=9, 2Hz), 7.89 (1H, d, J=15Hz)

5) rac-N-(1,2-Diphenylethyl)-2-butoxycinnamamide
mp : 163-164.5°C
NMR ($CDCl_3$, δ) : 0.97 (3H, t, J=7Hz), 1.50 (2H, m),
1.82 (2H, q, J=7Hz), 3.19 (2H, d, J=7Hz),
4.00 (2H, t, J=7Hz), 5.40 (1H, dt, J=9, 7Hz),
5.85 (1H, d, J=9Hz), 6.48 (1H, d, J=15Hz),
6.89 (1H, d, J=9Hz), 7.05-7.40 (12H, m),
7.43 (1H, d, J=9Hz), 7.90 (1H, d, J=15Hz)

6) rac-N-[2-(4-Methylphenyl)-1-phenylethyl]-4-heptyloxycinnamamide
mp : 155-158°C
NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=7Hz), 1.27 (8H, m), 1.80 (2H, q, J=7Hz), 2.29 (3H, s), 3.15 (2H, d, J=7Hz), 3.97 (2H, t, J=7Hz), 5.40 (1H, dt, J=9, 7Hz), 5.82 (1H, d, J=9Hz), 6.20 (1H, d, J=15Hz), 6.88 (2H, d, J=9Hz), 7.00 (4H, m), 7.20-7.40 (5H, m), 7.39 (2H, d, J=9Hz), 7.54 (1H, d, J=15Hz)

7) rac-N-(1,2-Diphenylethyl)-2-butoxyphenylacetamide
mp : 139-141°C
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.30-1.49 (2H, m), 1.57-1.70 (2H, m), 2.84-3.05 (2H, m), 3.55 (2H, m), 3.87 (2H, t, J=7Hz), 5.22 (1H, dt, J=9, 7Hz), 6.13 (1H, d, J=9Hz), 6.75-7.32 (14H, m)

8) rac-N-(1,2-Diphenylethyl)-2-hexyloxyphenylacetamide
mp : 111-113.5°C
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.30 (6H, br s), 1.55-1.68 (2H, m), 2.85-3.07 (2H, m), 3.55 (2H, m), 3.87 (2H, t, J=7Hz), 5.23 (1H, dt, J=9, 7Hz), 6.17 (1H, d, J=9Hz), 6.73-7.32 (14H, m)

9) rac-N-(1,2-Diphenylethyl)-2-heptyloxyphenylacetamide
mp : 110.5-111.5°C
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.28 (10H, br s), 2.95 (2H, m), 3.56 (2H, m), 3.88 (2H, t, J=7Hz), 5.23 (1H, dt, J=9, 7Hz), 6.15 (1H, d, J=9Hz), 6.75-7.30 (14H, m)

10) rac-N-[2-(4-Methylphenyl)-1-phenylethyl]-2-heptyloxyphenylacetamide
mp : 102-104°C

NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.30 (8H, br s), 1.58-1.73 (2H, m), 2.26 (3H, s), 2.80-3.01 (2H, m), 3.47 (1H, d, J=15Hz), 3.62 (1H, d, J=15Hz), 3.88 (2H, t, J=7Hz), 5.20 (1H, dt, J=9, 7Hz), 6.14 (1H, d, J=9Hz), 6.68 (2H, d, J=9Hz), 6.82-6.98 (4H, m), 7.02-7.33 (7H, m)

11) rac-N-(1,2-Diphenylethyl)-4-(4-heptyloxyphenyl)-butyramide
mp : 110.5-111.5°C
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.30 (8H, br s), 1.69-1.91 (4H, m), 2.13 (2H, t, J=7Hz), 2.48 (2H, t, J=7Hz), 3.10 (2H, d, J=7Hz), 4.00 (2H, t, J=7Hz), 5.30 (1H, dt, J=9, 7Hz), 5.68 (1H, d, J=9Hz), 6.76-7.35 (14H, m)

12) rac-N-[2-(4-Methylphenyl)-1-phenylethyl]-2-octyloxyphenylacetamide
mp : 97-99.5°C
NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=7Hz), 1.29 (10H, br s), 1.59-1.72 (2H, m), 2.29 (3H, s), 2.79-3.00 (2H, m), 3.47 (1H, d, J=15Hz), 3.62 (1H, d, J=15Hz), 3.88 (2H, t, J=7Hz), 5.20 (1H, dt, J=9, 7Hz), 6.17 (1H, d, J=9Hz), 6.67 (2H, d, J=9Hz), 6.90 (4H, q, J=9Hz), 7.02-7.31 (7H, m)

13) rac-N-(1,2-Diphenylethyl)-4-octyloxycinnamamide
NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=7Hz), 1.28 (10H, br s), 1.65-1.85 (2H, m), 3.19 (2H, d, J=7Hz), 3.98 (2H, t, J=7Hz), 5.42 (1H, dt, J=9, 7Hz), 5.89 (1H, d, J=9Hz), 6.23 (1H, d, J=15Hz), 6.80-6.90 (3H, m), 7.04-7.43 (11H, m), 7.54 (1H, d, J=15Hz)

14) rac-N-[2-(4-Methylphenyl)-1-phenylethyl]-4-

octyloxycinnamamide
NMR ($CDCl_3$, δ) : 0.90 (3H, s), 1.31 (10H, br s), 1.73-1.85 (2H, m), 2.30 (3H, s), 3.15 (2H, d, J=7Hz), 3.98 (2H, t, J=7Hz), 5.40 (1H, dt, J=9, 7Hz), 5.84 (1H, d, J=9Hz), 6.22 (1H, d, J=15Hz), 6.86 (2H, d, J=9Hz), 7.00 (4H, q, J=9Hz), 7.23-7.30 (5H, m), 7.40 (2H, d, J=9Hz), 7.55 (1H, d, J=15Hz)

15) rac-N-(1,2-Diphenylethyl)-2-octyloxycinnamamide
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.30 (10H, br s), 1.78-1.90 (2H, m), 3.20 (2H, dd, J=7, 2Hz), 4.00 (2H, t, J=7Hz), 5.40 (1H, dt, J=9, 7Hz), 5.87 (1H, d, J=9Hz), 6.48 (1H, d, J=15Hz), 6.88 (2H, t, J=9Hz), 7.05-7.30 (11H, m), 7.45 (1H, dd, J=9, 2Hz), 7.89 (1H, d, J=15Hz)

16) rac-N-[2-(4-Methylphenyl)-1-phenylethyl]-2-octyloxycinnamamide
NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=7Hz), 1.29 (10H, br s), 1.76-1.90 (2H, m), 2.28 (3H, s), 3.25 (2H, d, J=7Hz), 3.99 (2H, t, J=7Hz), 5.39 (1H, dt, J=9, 7Hz), 5.84 (1H, d, J=9Hz), 6.48 (1H, d, J=15Hz), 6.84-7.07 (7H, m), 7.20-7.35 (5H, m), 7.45 (1H, dd, J=9, 2Hz), 7.89 (1H, d, J=15Hz)

17) rac-N-(1,2-Diphenylethyl)-2-dodecyloxyphenylacetamide
mp : 103-105°C
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.29 (18H, br s), 1.53-1.68 (2H, m), 2.84-3.07 (2H, m), 3.62 (1H, d, J=15Hz), 3.47 (1H, d, J=15Hz), 3.87 (2H, t, J=7Hz), 5.23 (1H, dt, J=9, 7Hz), 6.16 (1H, d, J=9Hz), 6.73-7.24 (14H, m)

18) rac-N-[2-(4-Methylphenyl)-1-phenylethyl]-2-

dodecyloxyphenylacetamide
mp : 105-107.5°C
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.28 (18H, br s), 1.60-1.80 (2H, m), 2.27 (3H, s), 2.79-3.00 (2H, m), 3.47 (1H, d, J=15Hz), 3.62 (1H, d, J=15Hz), 3.88 (2H, t, J=7Hz), 5.20 (1H, dt, J=9, 7Hz), 6.15 (1H, d, J=9Hz), 6.68 (2H, d, J=9Hz), 6.90 (4H, q, J=9Hz), 7.04-7.32 (7H, m)

19) rac-(E)-N-(1,2-Diphenylethyl)-2-(2-octenyloxy)-phenylacetamide
mp : 108-110°C
NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=7Hz), 1.30 (6H, br s), 1.98-2.10 (2H, m), 2.84-3.05 (2H, m), 3.47 (1H, d, J=15Hz), 3.62 (1H, d, J=15Hz), 4.40 (2H, d, J=7Hz), 5.22 (1H, dt, J=9, 7Hz), 5.50-5.85 (2H, m), 6.30 (1H, d, J=9Hz), 6.77-7.30 (14H, m)

20) rac-(E)-N-[2-(4-Methylphenyl)-1-phenylethyl]-2-(2-octenyloxy)phenylacetamide
mp : 108-108.5°C
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.30 (6H, br s), 2.00-2.10 (2H, m), 2.29 (3H, s), 2.79-3.01 (2H, m), 3.47 (1H, d, J=15Hz), 3.62 (1H, d, J=15Hz), 4.40 (2H, d, J=7Hz), 5.20 (1H, dt, J=9, 7Hz), 5.48-5.87 (2H, m), 6.26 (1H, d, J=9Hz), 6.69 (2H, d, J=7Hz), 6.85-7.30 (11H, m)

21) rac-N-(1,2-Diphenylethyl)-2-nonyloxyphenylacetamide
mp : 104-105°C
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.29 (14H, s), 2.83-3.04 (2H, m), 3.47 (1H, d, J=15Hz), 3.62 (1H, d, J=15Hz), 3.88 (2H, t, J=7Hz), 5.23 (1H, dt, J=9, 7Hz), 6.17 (1H, d, J=9Hz), 6.75-6.97 (4H, m), 7.02-7.25 (10H, m)

22) rac-N-[2-(4-Methylphenyl)-1-phenylethyl]-2-nonyloxyphenylacetamide
mp : 106.5-108.5°C
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.29 (14H, br s), 2.25 (3H, s), 2.80-3.02 (2H, m), 3.47 (1H, d, J=15Hz), 3.62 (1H, d, J=15Hz), 3.87 (2H, d, J=7Hz), 5.20 (1H, dt, J=9, 7Hz), 6.15 (1H, d, J=9Hz), 6.67 (2H, d, J=7Hz), 6.82-6.97 (4H, m), 7.03-7.25 (7H, m)

23) rac-N-[2-(4-Methylphenyl)-1-phenylethyl]-2-decyloxyphenylacetamide
mp : 111°C
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.38 (14H, s), 1.64 (2H, q, J=7Hz), 2.26 (3H, s), 2.84 (1H, dd, J=7, 15Hz), 2.96 (1H, dd, J=7, 15Hz), 3.47 (1H, d, J=15Hz), 3.62 (1H, d, J=15Hz), 3.87 (2H, t, J=7Hz), 5.20 (1H, dt, J=7, 8Hz), 6.14 (1H, d, J=8Hz), 6.66 (2H, d, J=8Hz), 6.83-6.96 (4H, m), 7.03-7.32 (7H, m)

24) rac-N-(1,2-Diphenylethyl)-2-decyloxyphenylacetamide
mp : 105-106.5°C
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.26 (14H, m), 1.63 (2H, m), 2.90 (1H, dd, J=7, 15Hz), 3.00 (1H, dd, J=7, 15Hz), 3.47 (1H, d, J=15Hz), 3.62 (1H, d, J=15Hz), 3.87 (2H, t, J=7Hz), 5.22 (1H, dt, J=7, 8Hz), 6.15 (1H, d, J=8Hz), 6.74-6.80 (2H, m), 6.85 (1H, d, J=8Hz), 6.94 (1H, d, J=8Hz), 7.02-7.32 (10H, m)

25) rac-N-[2-(4-Methylphenyl)-1-phenylethyl]-2-heptyloxycinnamamide
mp : 166-167°C
NMR (DMSO-$d_6$, δ) : 0.85 (3H, t, J=7Hz), 1.22-1.44

(8H, m), 1.76 (2H, m), 2.23 (3H, s), 2.97 (2H, d, J=8Hz), 4.01 (2H, t, J=7Hz), 5.13 (1H, dt, J=8, 8Hz), 6.64 (1H, d, J=16Hz), 6.92-7.52 (13H, m), 7.62 (1H, d, J=16Hz), 8.59 (1H, d, J=8Hz)

26) rac-N-[2-(4-Methylphenyl)-1-phenylethyl]-2-hexyloxyphenylacetamide
mp : 88°C
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.25-1.41 (6H, m), 1.64 (2H, m), 2.27 (3H, s), 2.84 (1H, dd, J=7, 14Hz), 2.96 (1H, dd, J=7, 14Hz), 3.46 (1H, d, J=15Hz), 3.62 (1H, d, J=15Hz), 3.87 (2H, t, J=7Hz), 5.21 (1H, dt, J=7, 8Hz), 6.13 (1H, d, J=8Hz), 6.67 (2H, d, J=8Hz), 6.84-7.32 (11H, m)

27) rac-N-[2-(4-Methylphenyl)-1-phenylethyl]-3-(2-hexyloxyphenyl)propionamide
mp : 98°C
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.28-1.51 (6H, m), 1.76 (2H, q, J=7Hz), 2.27 (3H, s), 2.46 (2H, t, J=7Hz), 2.90 (2H, t, J=7Hz), 2.95 (2H, d, J=7Hz), 3.93 (2H, t, J=7Hz), 5.22 (1H, dt, J=7, 7Hz), 5.70 (1H, d, J=7Hz), 6.80-6.86 (4H, m), 6.97-7.31 (9H, m)

28) rac-N-(1,2-Diphenylethyl)-3-(2-hexyloxyphenyl)-propionamide
mp : 96°C
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.29-1.52 (6H, m), 1.76 (2H, q, J=7Hz), 2.46 (2H, t, J=7Hz), 2.89 (2H, t, J=7Hz), 3.02 (2H, d, J=7Hz), 3.93 (2H, t, J=7Hz), 5.25 (1H, dt, J=7, 8Hz), 5.69 (1H, d, J=8Hz), 6.80-7.29 (14H, m)

29) rac-N-(1,2-Diphenylethyl)-3-(4-hexyloxyphenyl)-propionamide

mp : 107.5°C
NMR ($CDCl_3$, δ) : 0.91 (3H, t, J=7Hz), 1.30-1.52 (6H, m), 1.75 (2H, q, J=7Hz), 2.41 (2H, t, J=7Hz), 2.82 (2H, t, J=7Hz), 3.03 (2H, d, J=7Hz), 3.90 (2H, t, J=7Hz), 5.25 (1H, dt, J=7, 7Hz), 5.63 (1H, d, J=7Hz), 6.77 (2H, d, J=8Hz), 6.93-7.31 (12H, m)

30) rac-N-[2-(4-Methylphenyl)-1-phenylethyl]-3-(4-hexyloxyphenyl)propionamide
mp : 130.5°C
NMR ($CDCl_3$, δ) : 0.91 (3H, t, J=7Hz), 1.29-1.48 (6H, m), 1.76 (2H, q, J=7Hz), 2.29 (3H, s), 2.40 (2H, t, J=7Hz), 2.82 (2H, t, J=7Hz), 2.99 (2H, d, J=7Hz), 3.92 (2H, t, J=7Hz), 5.23 (1H, dt, J=7, 7Hz), 5.63 (1H, d, J=7Hz), 6.75-6.85 (4H, m), 6.99-7.10 (6H, m), 7.22-7.31 (3H, m)

31) rac-(Z)-N-(1,2-Diphenylethyl)-3-[4-(1-undecenyl)phenyl]propionamide
mp : 90-91.5°C
NMR ($CDCl_3$, δ) : 0.87 (3H, t, J=7Hz), 1.26 (14H, br s), 2.30 (2H, m), 2.43 (2H, t, J=7Hz), 2.87 (2H, t, J=7Hz), 3.05 (2H, d, J=7Hz), 5.28 (1H, dt, J=9, 7Hz), 5.64 (2H, m), 6.38 (1H, d, J=11Hz), 6.92-7.25 (14H, m)

32) rac-(Z)-N-[2-(4-Methylphenyl)-1-phenylethyl]-3-[4-(1-undecenyl)phenyl]propionamide
mp : 87-89°C
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.29 (14H, br s), 2.25-2.38 (2H, m), 2.30 (3H, s), 2.44 (2H, t, J=7Hz), 2.99 (2H, t, J=7Hz), 3.00 (2H, d, J=7Hz), 5.24 (1H, dt, J=9, 7Hz), 5.58-5.72 (2H, m), 6.37 (1H, d, J=11Hz), 6.82-7.28 (13H, m)

33) rac-(Z)-N-(1,2-Diphenylethyl)-3-[4-(1-octenyl)-phenyl]propionamide
mp : 89-91°C
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.30 (8H, br s), 2.18-2.38 (2H, m), 2.47 (2H, t, J=7Hz), 2.89 (2H, t, J=7Hz), 3.07 (2H, d, J=7Hz), 5.28 (1H, dt, J=9, 7Hz), 5.57-5.70 (2H, m), 6.36 (1H, d, J=11Hz), 6.95-7.27 (14H, m)

34) rac-(Z)-N-[2-(4-Methylphenyl)-1-phenylethyl]-3-[4-(1-octenyl)phenyl]propionamide
mp : 92-94°C
NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=7Hz), 1.28 (8H, br s), 2.30 (3H, s), 2.15-2.39 (2H, m), 2.44 (2H, t, J=7Hz), 2.90 (2H, t, J=7Hz), 3.00 (2H, d, J=7Hz), 5.25 (1H, dt, J=9, 7Hz), 5.59-5.72 (2H, m), 6.36 (1H, d, J=11Hz), 6.85 (2H, d, J=9Hz), 6.98-7.25 (11H, m)

35) rac-(Z)-N-(1,2-Diphenylethyl)-3-[4-(1-nonenyl)-phenyl]propionamide
mp : 95-98°C
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.29 (10H, br s), 2.27-2.38 (2H, m), 2.44 (2H, t, J=7Hz), 2.90 (2H, t, J=7Hz), 3.04 (2H, d, J=7Hz), 5.20-5.32 (1H, dt, J=9, 7Hz), 5.57-5.70 (2H, m), 6.37 (1H, d, J=11Hz), 6.94-7.30 (14H, m)

36) rac-(Z)-N-[2-(4-Methylphenyl)-1-phenylethyl]-3-[4-(1-nonenyl)phenyl]propionamide
mp : 72-74°C
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.29 (10H, br s), 2.29 (3H, s), 2.18-2.38 (2H, m), 2.42 (2H, t, J=7Hz), 2.89 (2H, t, J=7Hz), 2.99 (2H, d, J=7Hz), 5.23 (1H, dt, J=9, 7Hz), 5.58-5.70 (2H,

m), 6.36 (1H, d, J=11Hz), 6.85 (2H, d, J=9Hz), 6.98-7.29 (11H, m)

37) rac-N-(1,2-Diphenylethyl)-3-(4-decylthiophenyl)-propionamide
mp : 96-97°C
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.28 (16H, br s), 2.43 (2H, t, J=7Hz), 2.82-2.95 (4H, m), 3.05 (2H, d, J=7Hz), 5.27 (1H, dt, J=9, 7Hz), 5.65 (1H, d, J=9Hz), 6.96-7.24 (14H, m)
MASS (m/z) : 502 ($M^+ + 1$)

Example 3

To a stirred solution of 3-octyloxyphenylacetic acid (528 mg) in methylene chloride (15 ml) was added 1-hydroxybenzotriazole (270 mg) and N,N'-dicyclohexylcarbodiimide (412 mg) at ambient temperature and the mixture was stirred for 20 minutes at the same temperature. To this mixture was added a solution of rac-1,2-diphenylethylamine (396 mg) in methylene chloride (5 ml) dropwise at ambient temperature and the mixture was stirred for 1 hour at the same temperature. The resulting N,N'-dicyclohexylurea was removed by filtration. The filtrate was washed with 3% hydrochloric acid, saturated sodium bicarbonate solution and brine, and dried. Evaporation of solvent gave a residue which was recrystallized from n-hexane-ethyl acetate to give rac-N-(1,2-diphenylethyl)-3-octyloxyphenyl-acetamide (512 mg).

mp : 91-92°C
IR (Nujol) : 3300, 1640, 1580, 1520, 1260, 1150, 940, 750, 700 $cm^{-1}$
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.25-1.51 (10H, m), 1.71-1.88 (2H, m), 2.80-3.07 (2H, m), 3.50 (2H, s), 3.91 (2H, t,

J=7Hz), 5.21 (1H, q, J=7Hz), 5.72 (1H, d, J=7Hz), 6.68-7.32 (14H, m)

The following compounds (Examples 4-1) to 4-5)) were obtained according to a similar manner to that of Example 3.

Example 4

1) rac-N-(1,2-Diphenylethyl)-3-heptyloxycinnamamide
mp : 104-105°C
IR (Nujol) : 3320, 1655, 1615, 1520, 1250, 970, 760, 700 $cm^{-1}$
NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=7Hz), 1.28-1.50 (8H, m), 1.70-1.82 (2H, m), 3.19 (2H, d, J=7Hz), 3.93 (2H, t, J=7Hz), 5.40 (1H, q, J=7Hz), 5.92 (1H, d, J=7Hz), 6.32 (1H, d, J=15Hz), 6.83-7.37 (14H, m), 7.53 (1H, d, J=15Hz)

2) rac-N-(1,2-Diphenylethyl)-4-octyloxyphenylacetamide
mp : 146-147°C
IR (Nujol) : 3300, 1640, 1605, 1505, 1300, 1240, 1175, 750, 700 $cm^{-1}$
NMR ($CDCl_3$, δ) : 0.85 (3H, t, J=7Hz), 1.30-1.52 (10H, m), 1.73-1.90 (2H, m), 2.80-3.08 (2H, m), 3.46 (2H, s), 3.98 (2H, t, J=7Hz), 5.21 (1H, q, J=7Hz), 5.67 (1H, d, J=7Hz), 6.90-7.30 (14H, m)

3) rac-N-(1,2-Diphenylethyl)-2-octyloxyphenylacetamide
mp : 107-108°C
IR (Nujol) : 3300, 1640, 1530, 1240, 1110, 1040, 740, 700 $cm^{-1}$
NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=7Hz), 1.12-1.45 (10H, m), 1.65 (2H, t, J=7Hz),

2.83-3.05 (2H, m), 3.45 (1H, d, J=15Hz), 3.63 (1H, d, J=15Hz), 3.88 (2H, t, J=7Hz), 5.21 (1H, q, J=7Hz), 6.12 (1H, d, J=7Hz), 6.75-7.37 (14H, m)

4) rac-N-(1,2-Diphenylethyl)-4-nonyloxybenzamide
mp : 117-119°C
IR (Nujol) : 3340, 1625, 1605, 1530, 1500, 1305, 1240, 740, 700 $cm^{-1}$
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.07-1.48 (10H, m), 1.65-1.98 (4H, m), 3.22 (2H, d, J=7Hz), 3.97 (2H, t, J=7Hz), 5.45 (1H, q, J=7Hz), 6.32 (1H, d, J=7Hz), 6.85 (2H, d, J=8Hz), 7.07-7.35 (10H, m), 7.63 (2H, d, J=8Hz)

5) rac-N-(1,2-Diphenylethyl)-4-decyloxyphenylacetamide
mp : 136-138°C
IR (Nujol) : 3300, 1640, 1530, 1510, 1240, 1180, 750, 700 $cm^{-1}$
NMR ($CDCl_3$, δ) : 0.87 (3H, t, J=7Hz), 1.20-1.53 (12H, m), 1.72-1.97 (4H, m), 2.80-3.08 (2H, m), 3.45 (2H, s), 3.95 (2H, t, J=7Hz), 5.27 (1H, q, J=7Hz), 5.70 (1H, d, J=7Hz), 6.85-7.28 (14H, m)

Example 5

A mixture of rac-N-(1,2-diphenylethyl)-3-heptyloxycinnamamide (200 mg) and 10% palladium on carbon (30 mg) in methanol (30 ml) was hydrogenated at ambient temperature at 1 atmospheric pressure for 5 hours. The catalyst was filtered and washed with methanol. The filtrate was evaporated. The residue was recrystallized from ethanol to give rac-N-(1,2-diphenylethyl)-3-(3-heptyloxyphenyl)propionamide (74 mg).

mp : 94-96°C
IR (Nujol) : 3320, 1640, 1600, 1530, 1250, 1170, 750, 700 $cm^{-1}$
NMR ($CDCl_3$, δ): 0.89 (3H, t, J=7Hz), 1.22-1.50 (8H, m), 1.68-1.81 (2H, m), 2.40 (2H, t, J=7Hz), 2.90 (2H, t, J=7Hz), 3.02 (2H, d, J=7Hz), 3.90 (2H, t, J=7Hz), 5.26 (1H, q, J=7Hz), 5.60 (1H, d, J=7Hz), 6.70-7.32 (14H, m)

The following compounds (Examples 6-1) to 6-12)) were obtained according to a similar manner to that of Example 5.

Example 6

1) rac-N-(1,2-Diphenylethyl)-3-(2-heptyloxyphenyl)-propionamide
mp : 93.5-94.5°C
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.30 (8H, m), 1.80 (2H, q, J=7Hz), 2.46 (2H, t, J=7Hz), 2.90 (2H, t, J=7Hz), 3.04 (2H, d, J=7Hz), 3.95 (2H, t, J=7Hz), 5.26 (1H, dt, J=9, 7Hz), 5.68 (1H, d, J=9Hz), 6.80-7.23 (14H, m)

2) rac-N-(1,2-Diphenylethyl)-3-(4-heptyloxyphenyl)-propionamide
mp : 98-100°C
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.30 (8H, m), 1.79 (2H, q, J=7Hz), 2.38 (2H, t, J=7Hz), 2.80 (2H, t, J=7Hz), 3.05 (2H, d, J=7Hz), 3.90 (2H, t, J=7Hz), 5.27 (1H, dt, J=9, 7Hz), 5.60 (1H, d, J=9Hz), 6.77 (2H, d, J=9Hz), 6.94-7.10 (8H, m), 7.13-7.25 (4H, m)

3) rac-N-(1,2-Diphenylethyl)-3-(4-decyloxyphenyl)-propionamide

NMR ($CDCl_3$, δ) : 0.99 (3H, t, J=7Hz), 1.30 (14H, m), 1.78 (2H, q, J=7Hz), 2.40 (2H, t, J=7Hz), 2.85 (2H, t, J=7Hz), 3.05 (2H, d, J=7Hz), 3.90 (2H, t, J=7Hz), 5.25 (1H, dt, J=9, 7Hz), 5.60 (1H, d, J=9Hz), 6.80 (2H, d, J=9Hz), 6.95-7.30 (12H, m)

4) rac-N-(1,2-Diphenylethyl)-3-(2-decyloxyphenyl)-propionamide
mp : 93-95°C
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.28 (14H, m), 1.77 (2H, q, J=7Hz), 2.48 (2H, t, J=7Hz), 2.90 (2H, t, J=7Hz), 3.02 (2H, d, J=9Hz), 3.93 (2H, t, J=7Hz), 5.35 (1H, dt, J=9, 7Hz), 5.68 (1H, d, J=9Hz), 6.80-7.24 (14H, m)

5) rac-N-(1,2-Diphenylethyl)-3-(2-butoxyphenyl)-propionamide
mp : 129-130°C
NMR ($CDCl_3$, δ) : 1.00 (3H, t, J=7Hz), 1.50 (2H, m), 1.78 (2H, q, J=7Hz), 2.48 (2H, t, J=7Hz), 2.90 (2H, t, J=7Hz), 3.04 (2H, d, J=7Hz), 3.96 (2H, t, J=7Hz), 5.25 (1H, dt, J=7, 9Hz), 5.59 (1H, d, J=9Hz), 6.79-6.88 (2H, m), 6.91-6.98 (2H, m), 7.05-7.25 (10H, m)

6) rac-N-[2-(4-Methylphenyl)-1-phenylethyl]-3-(4-heptyloxyphenyl)propionamide
mp : 119-122°C
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.30 (8H, m), 1.78 (2H, q, J=7Hz), 2.30 (3H, s), 2.40 (2H, t, J=7Hz), 2.83 (2H, t, J=7Hz), 3.00 (2H, d, J=7Hz), 3.93 (2H, t, J=7Hz), 5.25 (1H, dt, J=9, 7Hz), 5.60 (1H, d, J=9Hz), 6.75-6.88 (4H, m), 6.98-7.10 (6H, m), 7.00-7.25 (3H, m)

7) rac-N-(1,2-Diphenylethyl)-3-(4-octyloxyphenyl)-propionamide
mp : 79-81°C
NMR ($CDCl_3$, δ) : 0.90 (3H, t, J=7Hz), 1.30 (10H, br s), 1.68-1.84 (2H, m), 2.40 (2H, t, J=7Hz), 2.82 (2H, t, J=7Hz), 3.03 (2H, d, J=7Hz), 3.90 (2H, t, J=7Hz), 5.26 (1H, dt, J=9, 7Hz), 5.67 (1H, d, J=9Hz), 6.74-7.28 (14H, m)

8) rac-N-[2-(4-Methylphenyl)-1-phenylethyl]-3-(4-octyloxyphenyl)propionamide
mp : 113-114.5°C
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.30 (10H, br s), 1.70 - 1.83 (2H, m), 2.92 (3H, s), 2.40 (2H, t, J=7Hz), 2.85 (2H, t, J=7Hz), 2.99 (2H, d, J=7Hz), 3.92 (2H, t, J=7Hz), 5.24 (1H, dt, J=9, 7Hz), 5.61 (1H, d, J=9Hz), 6.75-7.22 (13H, m)

9) rac-N-(1,2-Diphenylethyl)-3-(2-octyloxyphenyl)-propionamide
mp : 77-79°C
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.30 (10H, br s), 1.71-1.85 (2H, m), 2.48 (2H, t, J=7Hz), 2.90 (2H, t, J=7Hz), 3.02 (2H, d, J=7Hz), 3.94 (2H, t, J=7Hz), 5.25 (1H, dt, J=9, 7Hz), 5.72 (1H, d, J=9Hz), 6.80-7.30 (14H, m)

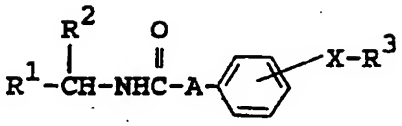
10) rac-N-[2-(4-Methylphenyl)-1-phenylethyl]-3-(2-octyloxyphenyl)propionamide
mp : 103.5-106°C
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.29 (10H, br s), 1.72-1.85 (2H, m), 2.28 (3H, s), 2.46 (2H, t, J=7Hz), 2.90 (2H, t, J=7Hz), 2.98 (2H, d, J=7Hz), 3.95 (2H, t, J=7Hz), 5.23 (1H, dt, J=9, 7Hz), 5.68 (1H, d, J=9Hz), 6.81-7.34 (11H, m)

11) rac-N-[2-(4-Methylphenyl)-1-phenylethyl]-3-(2-heptyloxyphenyl)propionamide
mp : 67-68.5°C
NMR ($CDCl_3$, δ) : 0.89 (3H, t, J=7Hz), 1.31-1.47 (8H, m), 1.78 (2H, m), 2.28 (3H, s), 2.46 (2H, t, J=7Hz), 2.90 (2H, t, J=7Hz), 2.97 (2H, t, J=7Hz), 3.93 (2H, t, J=7Hz), 5.22 (1H, dt, J=7, 7Hz), 5.67 (1H, d, J=7Hz), 6.80-7.27 (13H, m)

12) rac-N-(1,2-Diphenylethyl)-3-(4-undecylphenyl)-propionamide
mp : 101-102°C
NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=7Hz), 1.25 (18H, br s), 2.44 (2H, t, J=7Hz), 2.58 (2H, t, J=7Hz), 2.87 (2H, t, J=7Hz), 3.05 (2H, d, J=7Hz), 5.26 (1H, dt, J=9, 7Hz), 5.60 (1H, d, J=9Hz), 6.93-7.25 (14H, m)

CLAIMS

1. A compound of the formula :



(I)

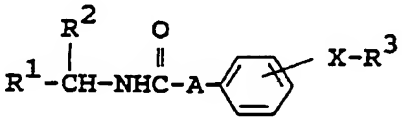
wherein $R^1$ is ar(lower)alkyl,
$R^2$ is aryl,
$R^3$ is alkyl or alkenyl,
A is a single bond, lower alkylene or lower alkenylene, and
X is O, S or a single bond.

2. A compound according to claim 1, wherein $R^3$ is higher alkyl,
A is lower alkylene, and
X is O.

3. A compound according to claim 2, wherein $R^1$ is benzyl or tolylmethyl,
$R^2$ is phenyl,
$R^3$ is heptyl, octyl, nonyl, decyl, undecyl or dodecyl, and
A is methylene or ethylene.

4. A compound of claim 3, which is rac-N-(1,2-diphenylethyl)-2-octyloxyphenylacetamide.

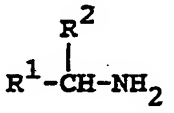
5. A process for preparing a compound of the formula :



(I)

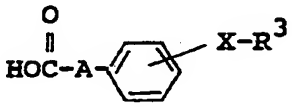
wherein $R^1$ is ar(lower)alkyl,
$R^2$ is aryl,
$R^3$ is alkyl or alkenyl,
A is a single bond, lower alkylene or lower alkenylene, and
X is O, S or a single bond,
which comprises,

a) reacting a compound of the formula :



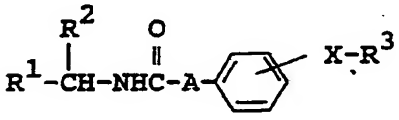
(II)

or its salt with a compound of the formula :



(III)

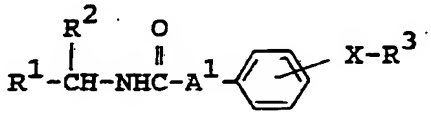
or its reactive derivative at the carboxy group to provide a compound of the formula :



(I)

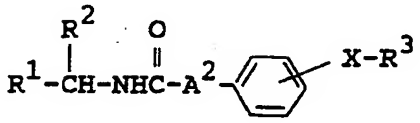
in the above formulas, $R^1$, $R^2$, $R^3$, A and X are each as defined above, or

b) subjecting a compound of the formula :



(Ia)

to reduction to provide a compound of the formula :



(Ib)

in the above formulas, $R^1$, $R^2$, $R^3$ and X are each as defined above, $A^1$ is lower alkenylene, and $A^2$ is lower alkylene.

6. A pharmaceutical composition comprising a compound of claim 1, as an active ingredient, in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

7. A compound of claim 1 for use as a medicament.

8. A method for therapeutic treatment of hypercholesterolemia, hyperlipidemia, atherosclerosis or diseases caused thereby which comprises administering an effective amount of a compound of claim 1 to human beings or animals.

9. Use of a compound of claim 1 for the manufacture of a medicament for treating hypercholesterolemia, hyperlipidemia, atherosclerosis or diseases caused thereby.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/JP 91/01556

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07C235/34; A61K31/165; C07C235/46; C07C323/61
C07C233/11

## II. FIELDS SEARCHED

Minimum Documentation Searched[7]

| Classification System | Classification Symbols |
|---|---|
| Int.Cl. 5 | C07C ; A61K |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

## III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

| Category[10] | Citation of Document,[11] with indication, where appropriate, of the relevant passages[12] | Relevant to Claim No.[13] |
|---|---|---|
| X | PESTICIDE BIOCHEMISTRY AND PHYSIOLOGY vol. 34, no. 3, 3 July 1989, pages 255 - 276; G.A.WHITE: 'SUBSTITUTED 2-METHYLBENZANILIDES AND STRUCTURALLY RELATED CARBOXAMIDES: INHIBITION OF COMPLEX II ACTIVITY IN MITOCHONDRIA FROM A WILD-TYPE STRAIN AND A CARBOXIN-RESISTANT MUTANT STRAIN OF USTILAGO MAIDIS' see page 255 - page 256; example XXXVII --- | 1-5 |
| A | US,A,3 784 577 (V.G.DE VRIES ET AL.) 8 January 1974 cited in the application see the whole document --- | 1-9 |
| A | US,A,4 603 145 (V.G. DE VRIES ET AL) 29 July 1986 see claims --- | 1-9 |
| | -/-- | |

* Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 28 FEBRUARY 1992 | 12. 05. 92 |
| **International Searching Authority** | **Signature of Authorized Officer** |
| EUROPEAN PATENT OFFICE | SANCHEZ Y GARCIA J. |

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

| Category ° | Citation of Document, with indication, where appropriate, of the relevant passages | Relevant to Claim No. |
|---|---|---|
| A | CHEMICAL ABSTRACTS, vol. 105, no. 21, 24 November 1996, Columbus, Ohio, US; abstract no. 190968D, 'TRISUBSTITUTED 3-(4-TOLYL)-1,2,3,4-TETRAHYDROISOQUINOLINES AND THEIR SALTS' page 718 ; see abstract & CS,A,225 598 (VALENTA V. ET AL.) 30 September 1985 --- | 1-9 |
| A | CHEMICAL ABSTRACTS, vol. 96, no. 9, 1 March 1982, Columbus, Ohio, US; abstract no. 68196F, 'STEREOCHEMICAL STUDIES.LII.CHIRAL AMIDES OF O-HYDROXY- AND O-METHOXY-SUBSTITUTED BENZOIC ACIDS' page 543 ; see abstract & ZH. ORG. KHIM. vol. 17, no. 6, 1981, pages 1241 - 1248; --- | 1-9 |

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. JP 9101556 SA 53324

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 28/02/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| US-A-3784577 | 08-01-74 | None | |
| US-A-4603145 | 29-07-86 | None | |
| CS-A-225598 | | None | |